

DATE: May 13, 1999

SUBJECT: **CHLORETHOXYFOS: Acute and Chronic Dietary Exposure Analysis.** Chemical #: 129006. DP Barcode: D255686.

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Action Requested

Provide refined Tier 3 acute and Tier 2 chronic dietary exposure analyses of the organophosphate, chlorethoxyfos, for use on corn that is supported through reregistration. The acute Tier 3 probabilistic analysis should include one-half the limit of detection ($\frac{1}{2}$ LOD = 0.005 ppm) based upon non-detectable chlorethoxyfos residues (<0.01 ppm) measured in field corn, pop corn, and sweet corn commodities) for residue values and Biological Economic Analysis Division's (BEAD's) percent crop treated data (% CT). The chronic Tier 2 analysis should include tolerance level residues and % CT data.

Executive Summary

Because chlorethoxyfos is an organophosphate, acute and chronic dietary risk concerns using the Dietary Exposure Evaluation Model (DEEM™) prompted HED to conduct the Tier 3 acute probabilistic and Tier 2 chronic dietary risk analyses. Refined acute and chronic dietary risk estimates associated with the consumption of chlorethoxyfos residues in food **did not exceed HED's level of concern** for any population subgroup from acute or chronic dietary exposure.

Toxicological Information

Table 1 provides a summary of toxicological endpoints for use in human risk assessments. A detailed description of the rationale for selection of the doses and endpoints can be found in the Hazard Identification Assessment Review Committee (HIARC) report (HIARC Document, 10/19/98).

For the acute dietary exposure risk assessment, the dose selected was the No Observed Adverse Effect Level (NOAEL) of 0.06 mg/kg/day based on plasma cholinesterase inhibition seen on day 3 in a 6-month ocular toxicity study in dogs. The uncertainty factor used to calculate the acute reference dose (RfD) was 100x. This included 10x for inter-species extrapolation and 10x for intra-species variation, resulting in an acute RfD of 0.0006 mg/kg. The risk assessment is required for the general U.S. population including infants and children.

For the chronic dietary exposure risk assessment, the dose selected was the NOAEL of 0.061 mg/kg/day based on overall cholinesterase inhibition seen in the 90-day, 6-month and 1-year studies in dogs. The uncertainty factor used to calculate the chronic reference dose (RfD) was 100x. This included 10x for inter-species extrapolation and 10x for intra-species variation, resulting in a chronic RfD of 0.0006 mg/kg/day. The risk assessment is required for the general U.S. population including infants and children.

The additional 10x factor for the protection of infants and children as required by the Food Quality Protection Act (FQPA) of 1996 was removed from the acute and chronic RfD based on the: 1) completeness of the toxicology database; 2) lack of increased susceptibility in developmental and reproductive toxicity studies; 3) use of adequate data (actual, surrogate, and/or modeling outputs) to satisfactorily assess dietary exposure as well as screening level drinking water exposure assessment; and 4) there are no uses that could result in residential exposures (See FQPA Document, 8/6/98). Since HED removed the acute and chronic 10x safety factors, the acute and chronic RfDs are identical to the acute and chronic Population Adjusted Doses (PADs). Therefore, the acute PAD is 0.0006 mg/kg and the chronic PAD is 0.0006 mg/kg/day.

The toxicology database for chlorethoxyfos is complete. Chlorethoxyfos being acutely toxic via the oral, dermal and inhalation routes of exposure, is too toxic to test for eye and skin irritation,

and is not a dermal sensitizer. It did not cause organophosphate induced delayed neuropathy (OPIDN) in hens, nor did it cause neuropathology in rats following single oral doses. The principal toxicology effects in mice, rats, and dogs following subchronic and chronic oral (dietary) exposure was inhibition of plasma, erythrocyte and/or brain cholinesterase activity. Repeated dermal applications for 21-days resulted in inhibition of plasma, erythrocyte and brain cholinesterase activity. There was no evidence of carcinogenicity in mice and rats. Chlorethoxyfos was non mutagenic both in vivo and in vitro. Chlorethoxyfos is classified as a Group D chemical; not classifiable as to human carcinogenicity based on the lack of carcinogenic potential which is supported by the lack of mutagenic activity. There was no evidence of increased susceptibility of rat or rabbit fetuses following in utero exposure in prenatal developmental toxicity studies. No offspring toxicity was seen at the highest dose tested in the two-generation reproduction toxicity study. There was no evidence of abnormalities in the development of the fetal nervous system in these studies.

Table 1. Toxicology Endpoints Selected for Risk Assessments.

Exposure Duration	Exposure Route	Dose	Endpoint	Comments
Acute	Dietary	Acute PAD= 0.0006 mg/kg	Plasma cholinesterase	NOAEL=0.06 mg/kg/day based on plasma ChE inhibition seen on day 3 in 6-month ocular toxicity study in dogs and an Uncertainty Factor of 100 applied. No FQPA Safety Factor.
Chronic	Dietary	Chronic PAD= 0.0006 mg/kg/day	Overall Cholinesterase inhibition (ChEI)	NOAEL=0.061 mg/kg/day based on ChEI in the 90-day, 6-month and 1-year studies in dogs. An Uncertainty Factor of 100 applied. No FQPA Safety Factor.

Residue Information

Tolerances are established (40 CFR §180.486) for residues of chlorethoxyfos in corn commodities (field, sweet, and popcorn) at 0.01 ppm. Chlorethoxyfos is a granular soil insecticide used for the control of corn rootworms, wireworms, cutworms, seed corn maggot, white grubs and symphylans on corn (it is not registered on any other commodities).

The nature of residue in corn and animals is adequately understood (HED Committee Meeting held 4/11/95). The HED Metabolism Assessment Review Committee has concluded that the residue of concern is the parent compound, chlorethoxyfos. In the corn metabolism study, no residues of the parent were found in corn commodities even after treatment at a 10x rate (MRID 41290601).

Tolerances are not required at this time for residues in milk and livestock tissues. The metabolism of chlorethoxyfos in the goat was extensive. No significant residues of parent or its oxygen analog were found. All metabolites detected were the result of re-incorporation of radioactivity

into natural products (MRID 41290602 and 41736804).

Adequate field trial data were submitted to support the established tolerances (MRID 41736815 and 417368-18). Field trials also showed no residues (<0.01 ppm) of parent in any of the corn raw agricultural commodities analyzed. On the basis of the results from both wet and dry corn processing studies (MRID 41290616 and 41736819), HED concludes that no food/feed additive tolerances are required. Based upon non-detectable chlorethoxyfos residues measured in field corn, popcorn, and sweet corn commodities (<0.01 ppm) one-half the limit-of-detection ($\frac{1}{2}$ LOD = 0.005 ppm) was used for the anticipated residue values in the acute dietary exposure analysis. In the chronic dietary exposure analysis, the tolerance level residue value (0.01 ppm) was used. No tolerances for meat, fat, meat byproducts, milk, or eggs have been established or are necessary. Therefore, meat, fat, meat byproducts, milk, poultry and eggs were not included in the acute or chronic dietary risk assessment.

DEEM™ default processing factors were utilized in both the acute and chronic analyses. The latest % CT information was available from BEAD (electronic correspondence, 11/98, D. Herzi) and is summarized in Table 2 along with existing and reassessed tolerance levels.

Table 2. Tolerances, Percent Crop Treated and Tolerance Level Residues for Chlorethoxyfos.

Commodity	Current Tolerance (ppm)¹	Tolerance Reassessment (ppm)¹	% Crop Treated²
field corn grain	0.01 ppm	0.01 ppm	0.2% (defaulted to 1%)
field corn forage	0.01 ppm	0.01 ppm	0.2% (defaulted to 1%)
field corn fodder	0.01 ppm	0.01 ppm	0.2% (defaulted to 1%)
popcorn grain	0.01 ppm	0.01 ppm	0.2% (defaulted to 1%)
popcorn fodder	0.01 ppm	0.01 ppm	0.2% (defaulted to 1%)
sweet corn (K + CWHR)	0.01 ppm	0.01 ppm	0.5% (defaulted to 1%)
sweet corn forage	0.01 ppm	0.01 ppm	0.5% (defaulted to 1%)

1: According to Chlorethoxyfos Revised Short Format HED Chapter of the RED (S. Knizner, 1/8/99, D252055).

2: % Crop Treated Information from BEAD (D. Herzi, 11/98).

Results/Discussion

The Dietary Exposure Evaluation Model (DEEM™) analysis evaluated the dietary exposure based on individual consumption data from USDA 1989-1992 Nationwide Continuing Surveys of Food Intake by Individuals (CSFII). HED's level of concern for acute and chronic dietary risk is greater than 100% of the aPAD and cPAD. A complete list of acute and chronic dietary exposures for all subpopulations is presented in Attachment 2 and 5, respectively.

Subgroups in Tables 3 and 4 represent the highest dietary exposure for the U.S. population and respective subgroups (i.e., children, females, and the other general population subgroups).

Table 3. Acute Probabilistic Dietary Exposure Results for Chlorethoxyfos.

Subgroups	95th Percentile Exposure (% aPAD)	99th Percentile Exposure (% aPAD)	99.9th Percentile Exposure (% aPAD)
U.S. Population	0.000000 (0.03)	0.000000 (0.06)	0.000003 (0.5)
Non-nursing infants (< 1 year old)	0.000001 (0.08)	0.000001 (0.12)	0.000001 (0.2)
Children (1-6 years old)	0.000000 (0.06)	0.000001 (0.10)	0.000012 (2.0)
Females (13-19 years old/not pregnant/not nursing)	0.000000 (0.03)	0.000000 (0.04)	0.000001 (0.1)
Males (13-19 years old)	0.000000 (0.03)	0.000000 (0.06)	0.000005 (0.9)

Table 4. Chronic Dietary Exposure Results for Chlorethoxyfos.

Subgroups	Chronic Total Exposure (mg/kg/day)	Chronic Risk (% cPAD)
U.S. Population	0.000000	0.0%
Non-nursing infants (< 1 year old)	0.000000	0.1%
Children (1-6 years old)	0.000000	0.1%
Females (13-19 years old/not pregnant/not nursing)	0.000000	0.0%
Males (13-19 years old)	0.000000	0.0%

The results of the acute and chronic analyses indicate that the acute probabilistic and chronic

dietary risk estimates associated with the proposed uses of chlorethoxyfos are **below the Agency's level of concern** (< 100% aPAD; < 100% cPAD) for all population subgroups.

List of Attachments

Attachment 1: Acute Residue Information

Attachment 2: Acute DEEM™ Analysis (S. Law, 5/04/99)

Attachment 3: Acute Residue Distribution Files

Attachment 4: Chronic Residue Information

Attachment 5: Chronic DEEM™ Analysis (S. Law, 4/29/99)

cc: S. Law 5/13/99 (RRB3), S. Knizner 5/13/99 (RRB3), L. Richardson (CEB1)

RDI: Dietary SAC 5/4/99

S. Law: 821E,CM#2: (703)305-0783:7509C:RRB3

Attachment 1: Acute Residue Information

U. S. Environmental Protection Agency

Ver. 6.73

DEEM Acute analysis for CHLORETHOXYFOS

1989-92 data

Residue file name: C:\DEEM\CHLORETHOXYFOS\1296006Ra. R96

Adjust. #2 NOT used

Analysis Date 05-04-1999

Residue file dated:

05-04-1999/11:02:22/8

Reference dose (aRfD) = 0.0006 mg/kg bw/day

Comment: Tier 3: 1/2 LOD; %CT; No processing studies

RDF indices and file names for Monte Carlo Analysis

1 Corn.rdf

Food Crop	RESIDUE	RDF
Adj. FactorsCode		
Grp Food Name	(ppm)	# #1
#2		
237 15 Corn/pop	0.000050	0 1.000
1.000		
238 15 Corn/sweet	2.000000	1 1.000
1.000		
266 15 Corn grain-endosperm	0.000050	0 1.000
1.000		
267 15 Corn grain-bran	0.000050	0 1.000
1.000		
268 15 Corn grain/sugar/hfcs	0.000050	0 1.500
1.000		
289 15 Corn grain-oil	0.000050	0 1.000
1.000		
388 15 Corn grain/sugar-molasses	0.000050	0 1.500
1.000		

Attachment 2: Acute DEEM™ Analysis

U. S. Environmental Protection Agency

Ver. 6.73

DEEM ACUTE analysis for CHLORETHOXYFOS
(1989-92 data)

Residue file: 1296006Ra.R96

Adjustment

factor #2 NOT used.

Analysis Date: 05-04-1999/12:03:05

Residue file dated:

05-04-1999/11:02:22/8

Acute Reference Dose (aRfD) = 0.000600 mg/kg body-wt/day

MC iterations = 1000 MC list in residue file MC seed = 10

Run Comment: Tier 3: ½ LOD; %CT; No processing studies

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Summary calculations:

		95th Percentile		99th Percentile	
99.9th Percentile		Exposure	% aRfD	Exposure	% aRfD
Exposure	% aRfD				

U. S. pop - all seasons:					
		0.000000	0.03	0.000000	0.06
0.000003	0.47				
All infants (<1 year):					
		0.000000	0.08	0.000001	0.12
0.000001	0.19				
Nursing infants (<1 year):					
		0.000000	0.03	0.000000	0.04
0.000000	0.06				
Non-nursing infants (<1 yr):					
		0.000001	0.08	0.000001	0.12
0.000001	0.20				
Children (1-6 years):					
		0.000000	0.06	0.000001	0.10
0.000012	2.06				
Children (7-12 years):					

0.000009	1.49	0.000000	0.05	0.000000	0.07
Females (13+/preg/not nsg):					
0.000005	0.79	0.000000	0.02	0.000000	0.02
Females (13+/nursing):					
0.000005	0.81	0.000000	0.02	0.000000	0.04
Females (13-19 yrs/np/nn):					
0.000001	0.10	0.000000	0.03	0.000000	0.04
Females (20+ years/np/nn):					
0.000002	0.27	0.000000	0.02	0.000000	0.03
Females (13-50 years):					
0.000002	0.27	0.000000	0.02	0.000000	0.03
Males (13-19 years):					
0.000005	0.89	0.000000	0.03	0.000000	0.06
Males (20+ years):					
0.000002	0.35	0.000000	0.02	0.000000	0.03
Seniors (55+):					
0.000002	0.31	0.000000	0.02	0.000000	0.03

Attachment 3:Acute Residue Distribution Files

#1
CHLORETHOXYFOS SWEET CORN
TOTALZ = 99
TOTALFREQ = 1

1, 0.005

Attachment 4: Chronic Residue Information

U. S. Environmental Protection Agency
Ver. 6.74
DEEM Chronic analysis for CHLORETHOXYFOS
1989- 92 data
Residue file: C:\deem\CHLORETHOXYFOS\1296006Rc. r96
Adjust. #2 used
Analysis Date 04- 29- 1999 Residue file dated:
04- 29- 1999/15: 29: 15/8
Reference dose (RfD) = 0. 0006 mg/kg bw/day
Comment: 1% CT

Food Crop RESIDUE
Adj. Factors
Code Grp Food Name (ppm) #1
#2

237 15 Corn/pop 0. 010000 1. 000
0. 010
238 15 Corn/sweet 0. 010000 1. 000
0. 010
266 15 Corn grain- endosperm 0. 010000 1. 000
0. 010
267 15 Corn grain- bran 0. 010000 1. 000
0. 010
268 15 Corn grain/sugar/hfcs 0. 010000 1. 500
0. 010

289 15	Corn grain-oil	0.010000	1.000
0.010			
388 15	Corn grain/sugar-molasses	0.010000	1.500
0.010			

Attachment 5: Chronic DEEM™ Analysis

U. S. Environmental Protection Agency

Ver. 6.74

DEEM Chronic analysis for CHLORETHOXYFOS

(1989-92 data)

Residue file name: C:\deem\CHLORETHOXYFOS\1296006Rc. r96

Adjustment

factor #2 used.

Analysis Date 04-29-1999/15:29:51

Residue file dated:

04-29-1999/15:29:15/8

Reference dose (RfD, CHRONIC) = .0006 mg/kg bw/day

COMMENT 1: 1% CT

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Total exposure by population subgroup

Exposure Total

Percent of Population Subgroup	mg/kg body wt/day
Rfd	
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U. S. Population (total) 0.0%	0.000000
U. S. Population (spring season) 0.0%	0.000000
U. S. Population (summer season) 0.0%	0.000000
U. S. Population (autumn season) 0.0%	0.000000
U. S. Population (winter season) 0.0%	0.000000
Northeast region	0.000000

0.0%	
Midwest region	0.000000
0.0%	
Southern region	0.000000
0.0%	
Western region	0.000000
0.0%	
Hispanics	0.000000
0.0%	
Non-hispanic whites	0.000000
0.0%	
Non-hispanic blacks	0.000000
0.0%	
Non-hispanic/non-white/non-black)	0.000000
0.0%	
All infants (< 1 year)	0.000000
0.1%	
Nursing infants	0.000000
0.0%	
Non-nursing infants	0.000000
0.1%	
Children 1-6 yrs	0.000000
0.1%	
Children 7-12 yrs	0.000000
0.0%	
Females 13-19(not preg or nursing)	0.000000
0.0%	
Females 20+ (not preg or nursing)	0.000000
0.0%	
Females 13-50 yrs	0.000000
0.0%	
Females 13+ (preg/not nursing)	0.000000
0.0%	
Females 13+ (nursing)	0.000000
0.0%	
Males 13-19 yrs	0.000000
0.0%	
Males 20+ yrs	0.000000

0.0%		
Seniors 55+		0.000000
0.0%		
Pacific Region		0.000000
0.0%		
